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INTELLECTUAL PROPERTY INDIA

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GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
W - 5, WEST PATEL NAGAR
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application, Provisional Specification*** *and* ***Drawing Sheets*** *filed in connection with Application for Patent No.* ***1368/Del/2003*** *dated* ***7TH November 2003.*** ✓

Witness my hand this 24th day of January 2005.

M.R. Gupta

(M.R. GUPTA)
Assistant Controller of Patents & Designs

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

FORM 1 1368-DEL-03

THE PATENTS ACT, 1970
(39 of 1970)

17 NOV 2003

APPLICATION FOR GRANT OF A PATENT

(See Sections 5(2), 7, 54 and 135; and rule 39)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF HIGHLY PURE 3-(2-SUBSTITUTED VINYL) CEPHALOSPORIN"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. YATENDRA KUMAR
b. MOHAN PRASAD
c. KAPTAN SINGH
d. ASHOK PRASAD
e. SANTOSH RICHHARIYA

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon 122001 (Haryana), India, all Indian Nationals.

DUPLICATE

4. We claim the priority from the application(s) filed in convention countries, particulars of which are as follows: **NOT APPLICABLE.**

5. We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which we are the applicant: **NOT APPLICABLE**

6. We state that the application is divided out of our application, the particulars of which are given below and pray that this application deemed to have been filed on ..... Under section 16 of the Act. **NOT APPLICABLE**

7. That we are the assignee or legal representatives of the true and first inventors.

8. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon - 122001 (Haryana). INDIA.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10

9. Following declaration was given by the inventors or applicants in the convention country:

We, YATENDRA KUMAR, MOHAN PRASAD, KAPTAN SINGH, ASHOK PRASAD, SANTOSH RICHHARIYA of Ranbaxy Laboratories Limited, Plot No. 20, Sector - 18, Udyog Vihar Industrial Area, Gurgaon -122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention or applicant in the convention country declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a.

(YATENDRA KUMAR)

b.

(MOHAN PRASAD)

c.

(KAPTAN SINGH)

d.

(ASHOK PRASAD)

e.

(SANTOSH RICHHARIYA)

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Followings are the attachment with the application:
    a. Complete Specification (3 copies)
    b. Drawings (3 copies)
    c. Priority document(s)
    d. Statement and Undertaking on FORM – 3
    e. Power of Authority (Not required)
    f. Fee Rs.3,000/- (Rupees Three Thousand only..) in cheque bearing No. dated : drawn on HDFC Bank, New Delhi.

We request that a patent may be granted to us for the said invention.

Dated this 6TH day of **November, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

1568 DEL 03

FORM 2

7 NOV 2003

The Patents Act, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See Section 10)

A PROCESS FOR THE PREPARATION OF HIGHLY PURE 3-(2-SUBSTITUTED VINYL) CEPHALOSPORIN

ORIGINAL

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a process for preparation of highly pure amorphous and crystalline forms of 3-(2-substituted vinyl) cephalosporin.

Cefditoren pivoxil of Formula I as shown in the accompanied drawing (also called as ME-1207), which is pivaloxymethyl ester of cefditoren (also called as ME-1206), is a third generation cephalosporin derivative belonging to the class of 3-(2-substituted vinyl) cephalosporin which was first developed by Meiji Seika of Japan with the aim of producing active cephalosporins with potent and broad-spectrum activity (US Patent No 4,839, 350). Cefditoren pivoxil is highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria.

Cefditoren pivoxil of Formula I as shown in the accompanied drawing is chemically [6R-[3(Z),6a,7b(Z)]]-7-[[(2-Amino-4-thiazolyl)(methoxyimino)acetyl]amino]-3-[2-(4-methyl-5-thiazolyl)ethenyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-carboxylic acid, pivaloyloxy-methyl ester.

US Patent No 4,839, 350 describes a process for preparation of amorphous form of cefditoren pivoxil. The process described is non-selective and gives more than 20% of unwanted E-isomer which is then separated by means of column chromatography. The purity of cefditoren pivoxil obtained is typically around 94.0% to 95.5% when analyzed by HPLC.

US Patent No. 6,294,669 describes a crystalline substance of cefditoren pivoxil and process for preparing the same. The crystalline substance described has a purity of about 97 to 98%, typically 97.7% which is still not sufficient to incorporate it in a pharmaceutical composition due to presence of impurities. The process described for converting amorphous cefditoren pivoxil to the crystalline substance is very complicated. It requires eight steps which involve

dissolution, concentration, addition of two or three different solvents in different steps. Thus the conversion of amorphous form to crystalline form as described in this patent is time consuming, low yielding and difficult to scale at commercial level. In addition, the crystalline form of cefditoren pivoxil is not suitable for oral administration due to its poor solubility in water.

US Patent No. 6,342,493 describes a process for preparation of orally administrable, yellow and powdery compositions essentially consisting of particles composed of a homogeneous mixture of a crystallographically stable, amorphous and water soluble substance of cefditoren pivoxil with a water soluble high molecular weight polymer. The process involves mixing the crystalline cefditoren pivoxil and water soluble high molecular weight polymer in an acidic solution followed by basification of the acidic solution to precipitate the yellow coloured powdery composition containing amorphous cefditoren pivoxil having high molecular weight polymer. The process has lot of technical problem such as strict production control and requirement of skilled staff to carry out the operation. The process described does not give amorphous product which is free from any additive. Also, the amorphous material containing the additives has a limited application in pharmaceutical dosage forms.

Japanese Patent Application No. 2001-131071A2 describes process for preparation of amorphous cefditoren pivoxil by the processes such as precipitation, spray-drying, freeze-drying. It also describes a process of converting crystalline cefditoren pivoxil to amorphous cefditoren pivoxil by milling. The process described gives a product which has purity in the range of 93 to 98%. For precipitation, spray drying, freeze-drying, no particular form of cefditoren pivoxil is reported. The examples described in the patent specification suggests that it is the amorphous form of cefditoren pivoxil is used for spray-drying, freeze-drying or precipitation since crystalline form has negligible solubility at the specified volume in the given solvents.

In order to provide hereto unknown highly pure amorphous and crystalline forms of cefditoren pivoxil we embarked upon a new process which is simple, cost-effective, and easily scalable at commercial level. The highly pure, more stable amorphous form containing no additives has an outstanding demand and utility in the pharmaceutically acceptable dosage forms.

The term highly pure cefditoren pivoxil refers to cefditoren pivoxil in amorphous or crystalline form having purity not less than 98.5% containing less than 1.0% of E-isomer impurity and less than 1% of Δ^2-isomer impurity. More preferably the purity is not less than 99.0% which has less than 0.5% of E-isomer impurity and less than 0.5% of Δ^2-isomer impurity. Most preferably highly pure cefditoren pivoxil refers to cefditoren pivoxil having purity not less than 99.20% containing less than 0.1% of E-isomer impurity and less than 0.5% of Δ^2-isomer impurity.

First aspect of the present invention provides highly pure amorphous cefditoren pivoxil having purity greater than 98.5% containing less than 1.0% of unwanted E-isomer impurity and less than 1% of Δ^2-isomer impurity. The said amorphous form has the typical XRD pattern as depicted in Figure I of the accompanied drawing.

Second aspect provides a highly pure crystalline cefditoren pivoxil having purity greater than 98.5% containing less than 1.0% of unwanted E-isomer impurity and less than 1% of Δ^2-isomer impurity. The said crystalline form has the typical XRD pattern as depicted in Figure II.

Third aspect provides an efficient and one step process for preparation of crystalline cefditoren pivoxil from amorphous cefditoren pivoxil which comprises of

a) adding amorphous cefditoren pivoxil to an organic solvent optionally containing water.
b) crystallizing the product from the reaction mass.
c) isolating crystalline cefditoren pivoxil.

Amorphous cefditoren pivoxil is prepared according to the process described in our pending application No. 1004/DEL/2003. The said amorphous material was added to organic solvent optionally containing water or an organic solvent optionally containing water is added to amorphous material in optional order of succession. The resultant reaction mass was allowed to stir at a temperature of -20 to 100°C to complete crystallization. The crystalline material separated is then isolated from the reaction mass by conventional methods used in cephalosporin chemistry known to a person of ordinary skills. The said crystalline form has a typical XRD pattern as depicted in Figure II as shown in the accompanied drawing.

Organic solvent used for this aspect can be selected from ethanol, methanol, isopropyl alcohol, n-butanol, iso-butanol, amyl alcohol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, acetone, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, acetonitrile, tetrahydrofuran, 1,4-dioxane, propylene glycol, ethylene glycol, methylene chloride, ethylene chloride, chloroform or mixtures thereof. The said solvent can have up to 0.01 to 50% by weight of water.

Ideally the crystallization temperature is kept between 0 to 60°C. The isolated crystalline cefditoren pivoxil is then optionally dried under vacuum to get highly pure cefditoren pivoxil having purity greater than 98.5% wherein the unwanted E-isomer is less than 1.0% and less than 1% of Δ^2-isomer impurity.

Fourth aspect provides a process for preparation of highly pure amorphous form cefditoren pivoxil from crystalline cefditoren pivoxil which comprises of

a) dissolving crystalline cefditoren pivoxil in a suitable organic solvent.

b) adding a second organic solvent to the solution or solution to the second organic solvent in optional order of succession in order to precipitate cefditoren pivoxil

c) isolating the amorphous cefditoren pivoxil from the reaction mass.

Crystalline cefditoren pivoxil is dissolved in first organic solvent selected from a group comprising of water-immiscible or partially miscible solvents such as iso-butanol, n-butanol, ethyl formate, methyl acetate, ethyl acetate, butyl acetate, isobutyl acetate, methyl ethyl ketone, diisobutyl ketone, methyl isobutyl ketone, methylene chloride, ethylene chloride, chloroform or mixtures thereof and to the solution added second organic solvent selected from a group comprising of diisopropyl ether, diethyl ether, toluene, xylene, heptane, hexane, cyclohexane, cycloheptane, petroleum ether or mixtures thereof in optional order of succession to affect the precipitation of cefditoren pivoxil from the reaction mass. To enhance the precipitation common techniques such as seeding with amorphous material or cooling the reaction mass can also be effectively performed. The precipitated product is then isolated from the reaction mass and dried under vacuum to get amorphous form of cefditoren pivoxil having purity greater than 98.5% wherein the unwanted E-isomer is less than 1.0% and less than 1% of Δ^2-isomer impurity.

The dissolution crystalline cefditoren pivoxil in the said first organic solvent can be effected conveniently by initially dissolving crystalline cefditoren pivoxil in third organic solvent selected from a group comprising of dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or mixtures thereof. To this solution added water and a first organic solvent in optional order of succession to obtain a biphasic solution. The organic layer is then separated and may be washed successively with water to remove the traces of third organic solvent. A solution of crystalline cefditoren pivoxil in first organic solvent can thus be effectively prepared.

Fifth aspect provides a process for preparation of highly pure amorphous form of cefditoren pivoxil which comprises of

a) dissolving crystalline cefditoren pivoxil in suitable organic solvent.

b) removing the solvent from the reaction mass

c) isolating amorphous form of cefditoren pivoxil.

The suitable organic solvent is already described as first organic solvent in the fourth aspect of the invention. If required optional heating can be carried out to dissolve the crystalline form completely in the said organic solvent (s). The dissolution of crystalline cefditoren pivoxil in the suitable organic solvent can be affected by the method already described in the fourth aspect of the invention.

The concentration of the solvent can be carried out under vacuum of about 100 to 0.01 mm of Hg wherein the solvent is removed by vacuum distillation of the solution with optionally heating the solution at a temperature of about 0 to 100°C to effect faster removal of the solvent.

The solvent can also be removed by spray-drying the solution of crystalline cefditoren pivoxil using a spray-dryer. For the purpose of spray-drying, mini-spray Dryer (Model : Buchi 190 Switzerland) which operates on the principle of nozzle spraying in an parallel - flow i.e. the sprayed product and the drying gas flow in the same direction was used. The drying gas can be air or inert gases such as nitrogen, argon or carbon dioxide. Nitrogen is preferred in this case.

Sixth aspect of the present invention provides a process for preparing highly pure amorphous form of cefditoren pivoxil from crystalline form which comprises of

a) dissolving crystalline form of cefditoren pivoxil in organic solvent optionally containing water and

b) freeze drying or lyophilizing the said solution to get highly pure amorphous form of cefditoren pivoxil.

A solution of crystalline cefditoren pivoxil in organic solvent optionally containing water is prepared as described in fourth and fifth aspect of the invention. The clear solution is then freeze-dried by conventional techniques to get the amorphous cefditoren pivoxil. The amorphous form can then be dried under vacuum.

Seventh aspect provides a process for preparing highly pure amorphous form of cefditoren pivoxil from crystalline form which comprises of

a) dissolving the crystalline cefditoren pivoxil in an acid optionally in presence of an organic solvent
b) adding a water to the solution, such that cefditoren pivoxil precipitates out from the solution
c) isolating the highly pure amorphous cefditoren pivoxil from the mixture.

Crystalline cefditoren pivoxil is dissolved in an acid optionally containing a water-miscible organic solvent and the solution can be optionally treated with charcoal or clarified to remove foreign particulate matter. The clear solution can be obtained by gently warming the mixture as well. To the clear solution water is added at such a rate that cefditoren pivoxil precipitates very slowly. The mixture after complete addition of water can be chilled or partially concentrated to remove the organic solvent. The separated amorphous form is then filtered and dried as per the methods described earlier.

The acid is selected from organic acids comprising of C_{1-12} alkyl or aryl carboxylic acids and C_{1-10} alkyl or aryl sulphonic acids selected from formic acid, acetic acid, propionic acid, butyric acid, acrylic acid, benzoic acid, mono or di or tri substituted benzoic acids, phenyl acetic acid, substituted phenyl acetic acid, methanesulphonic acid, p-toluenesulphonic acid, benzenesulphonic acid and the like or mixture thereof. The acid can be inorganic acid selected

from a group comprising of hydrochloric acid, nitric acid, sulphuric acid, phosphoric acid and the like or mixtures thereof.

Water miscible organic solvent can be selected from a group comprising of dimethylformamide, dimethylacetamide, tetrahydrofuran, 1,4-dioxane, methanol, acetone, acetonitrile, ethanol, isopropanol or mixtures thereof.

Eighth aspect of the invention provides a process for converting a mixture of amorphous and crystalline form of cefditoren pivoxil to highly pure amorphous form of cefditoren pivoxil.

A mixture of amorphous and crystalline form of cefditoren pivoxil can be prepared directly from the reaction mixture or from the crystalline form or from the amorphous form of cefditoren pivoxil by the process already described in the specification with little variations in reaction temperature, quantity of solvent, reaction time, spray-drying temperature, flow rate of inert gas during spray-drying and the like.

The said mixture of amorphous and crystalline cefditoren pivoxil is then converted to the amorphous form by any of the techniques already described in the earlier aspects.

Ninth aspect relates to pharmaceutical compositions and dosage forms comprising highly pure amorphous or crystalline form of cefditoren pivoxil to be used as antibacterial in the treatment of infections caused by gram positive, gram negative and resistant strains of bacteria with a pharmaceutically acceptable carrier.

Tenth aspect of the invention relates to a method of treating infections caused by gram positive, gram negative and resistant strains of bacteria, comprising administering to a mammalian host in

need thereof a therapeutically effective amount of the highly pure amorphous or crystalline form of cefditoren pivoxil..

Figure I is X-ray powder diffraction (XRD) pattern of highly pure amorphous form of cefditoren pivoxil.

Figure II is X-ray powder diffraction (XRD) pattern of highly pure crystalline form of cefditoren pivoxil.

Figure III is X-ray powder diffraction (XRD) pattern of mixture of highly pure crystalline and amorphous cefditoren pivoxil.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLE 1

PREPARATION OF CEFDITOREN PIVOXIL (FORMULA I)

To a stirred mixture of Cefditoren sodium (20 g) in DMF (120 ml) at –15°C, iodomethyl pivalate (10 g) was added in one lot. Reaction mixture was stirred at -10 to - 15°C for 60 min. Subsequently it was quenched by pouring reaction mixture in DI water and ethyl acetate. Ethyl acetate layer was washed sequentially by water, 0.5% $NaHCO_3$ and 0.1% HCl and finally by water. Organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure till residual volume is about 100 ml.

This solution was slowly added to cyclohexane (600 ml) at ambient temperature and stirred for 30 min. The product was filtered under suction and dried under vacuum to get 18.8 g Cefditoren pivoxil.

Yield: 78% (XRD as per Figure I showed it to be an amorphous material)

HPLC Purity: 98.36%

E-isomer of Cefditoren pivoxil: 0.14%

Δ^2-isomer: 0.76%

IR in KBr (cm -1): 2974, 2934, 1787, 1752, 1678, 1534, 1369.

EXAMPLE 2

PREPARATION OF CRYSTALLINE CEFDITOREN PIVOXIL

Denatured spirit (150 ml) was added to product obtained in Example 1 (15 g) and the heterogeneous mixture was stirred at 30 – 35°C for 2 – 3 hrs for crystallization to complete. The product was filtered under suction and dried under vacuum to afford crystalline cefditoren pivoxil.

Yield: 13.5 g (XRD as per Figure II showed it to be crystalline material)

HPLC Purity: 99.23%

E-Isomer of Cefditoren pivoxil: 0.08%

Δ^2-isomer: 0.41%

IR in KBr (cm -1): 2961, 1785, 1736, 1724, 1620, 1529, 1372

EXAMPLE 3

PREPARATION OF CRYSTALLINE CEFDITOREN PIVOXIL

Product obtained in Example 1 (2.0 g) was suspended in aqueous ethanol (90% v/v, 20 ml) at about 30 – 32°C for 3.0 hrs to complete crystallization. Crystalline product was filtered and washed with aqueous ethanol (90%v/v, 5 ml) and dried at 35 - 40°C under vacuum to afford crystalline cefditoren pivoxil.

Yield: 1.7 g (XRD as per Figure II showed it to be crystalline material)

HPLC Purity: 98.61%

E-isomer of cefditoren pivoxil: 0.086%

Δ^2-isomer: 0.82%

IR in KBr (cm -1): 2961, 1785, 1736, 1724, 1620, 1529, 1372

EXAMPLE 4

PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Crystalline Cefditoren pivoxil (2.0 g) was dissolved in DMF (10 ml) at ambient temperature. This solution was added to pre-cooled ethyl acetate at 0 – 5°C. Solution was washed with water in three times. Ethyl acetate was concentrated under reduced pressure to get a solution of Cefditoren pivoxil about 250 mg / ml. This solution was added to cyclohexane (60 ml) slowly in 10 – 15 min at ambient temperature and stirred for 60 min. Solid was filtered.

HPLC Purity: 98.90%
E-Isomer of Cefditoren pivoxil: 0.15%
Δ^2-isomer: 0.69%
XRD as per Figure 1 showed it to be an amorphous material

EXAMPLE 5

PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Crystalline Cefditoren pivoxil (20.0 g) was dissolved in DMF (100 ml) at ambient temperature. This solution was added to pre-cooled mixture of ethyl acetate (600 ml) and water (400 ml) at 5 – 10°C. Resultant mixture was stirred for 10 to 15 minutes and the layers were separated. The solution was subjected to spray-drying using a mini spray-dryer (Buchi Model 190) at an inlet

temperature of 75°C and outlet temperature of 55°C with a feed rate of 15 ml per minute. Cefditoren pivoxil (15 g) was thus obtained in an amorphous form.

HPLC Purity: 99.04%

E-Isomer of Cefditoren pivoxil: 0.10%

Δ^2-isomer: 0.60%

XRD as per Figure I showed it to be an amorphous material.

EXAMPLE 6

PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Crystalline Cefditoren pivoxil (5.0 g) was dissolved in DMF (30 ml) at ambient temperature. This solution was added to pre-cooled mixture of ethyl acetate (150 ml) and water (100 ml) at 5 – 10°C. Resultant mixture was stirred for 10 to 15 minutes and the layers were separated. The organic layer was treated with activated charcoal and the mixture was filtered. The clear filtrate was concentrated under reduced pressure at 10-15°C to get a foam. The traces of the solvent were finally removed by vacuum distillation at 20-25°C at 5-10 mm of Hg to get amorphous cefditoren pivoxil 4.0 g).

HPLC Purity: 98.79%

E-Isomer of Cefditoren pivoxil: 0.13%

Δ^2-isomer: 0.59%

XRD as per Figure I showed it to be an amorphous material

EXAMPLE 7

PREPARATION OF AMORPHOUS CEFDITOREN PIVOXIL FROM CRYSTALLINE CEFDITOREN PIVOXIL

Step A: Preparation of mixture of crystalline and amorphous cefditoren pivoxil from crystalline cefditoren pivoxil

Crystalline Cefditoren pivoxil (2.0 g) was dissolved in acetic acid (4.0 ml) at ambient temperature. This solution was added to pre-cooled water (60 ml) at 5 - 10°C. Resultant mixture was stirred for 10 to 15 minutes at 5-10°C. The separated solids were filtered and washed with copious amount of water. The product was then dried to get (1.7 g) a mixture of crystalline and amorphous cefditoren pivoxil.

Step B: Conversion of mixture of crystalline and amorphous cefditoren pivoxil to amorphous cefditoren pivoxil

The product obtained in step A) (1.7 g) was dissolved in DMF (10 ml) at ambient temperature. This solution was added to pre-cooled mixture of ethyl acetate (50 ml) and water (35 ml) at 5 – 10°C. Resultant mixture was stirred for 10 to 15 minutes and the layers were separated. The organic layer obtained was subjected to spray-drying using a mini spray-dryer (Buchi Model 190) at an inlet temperature of 75°C and outlet temperature of 55°C with a feed rate of 15 ml per minute. Cefditoren pivoxil (1.45 g) was thus obtained in an amorphous form.

HPLC Purity: 98.64%
E-Isomer of Cefditoren pivoxil: 0.10%
Δ^2-isomer: 0.75%
XRD as per Figure I showed it to be an amorphous material.

Dated this 6TH day of **November, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

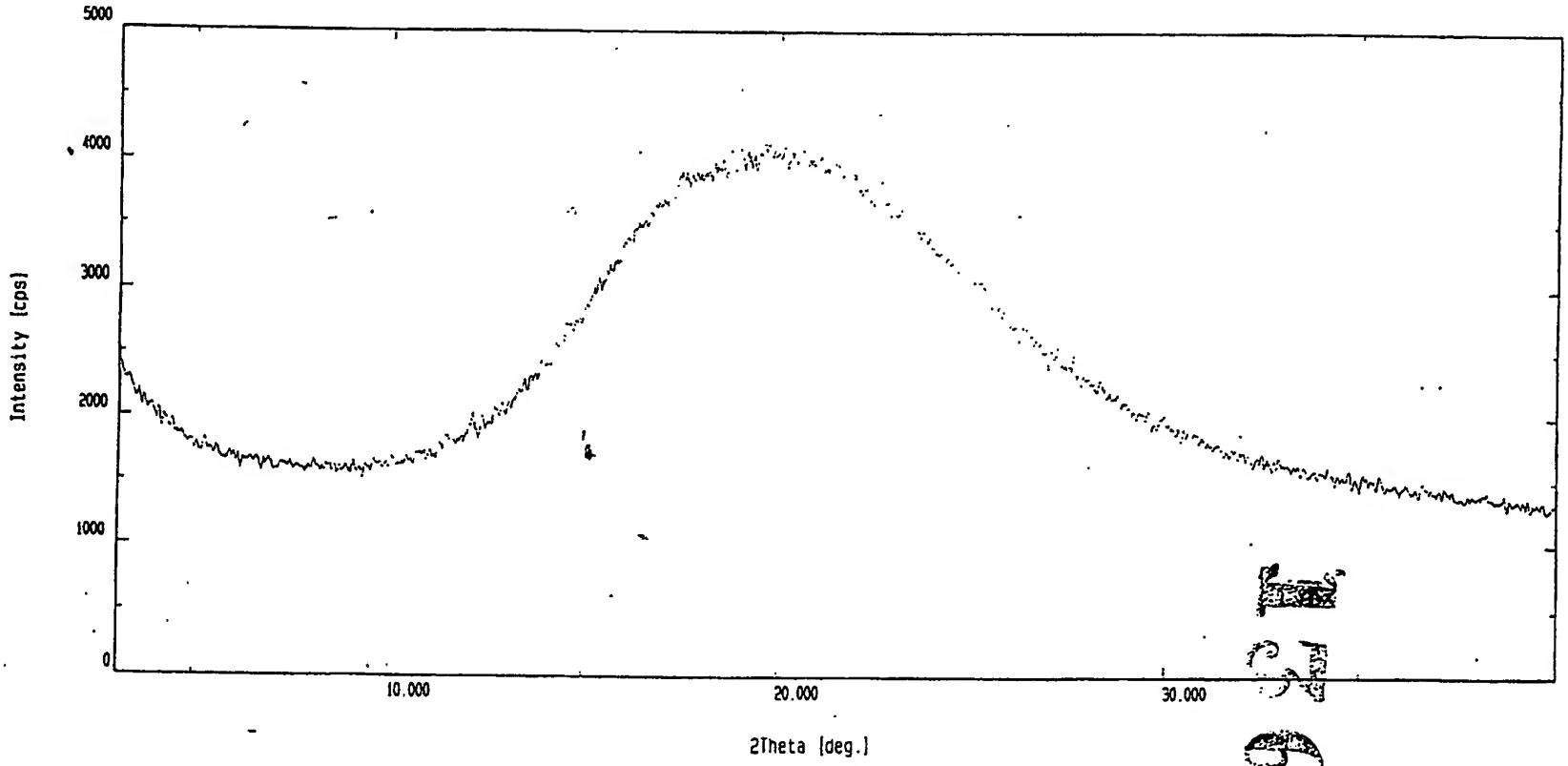
ABSTRACT

A PROCESS FOR THE PREPARATION OF HIGHLY PURE 3-(2-SUBSTITUTED VINYL) CEPHALOSPORIN

The present invention relates to a process for preparation of highly pure amorphous and crystalline forms of 3-(2-substituted vinyl) cephalosporin.

FIGURE I

ORIGINAL



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 04

Sheet 01 of 04

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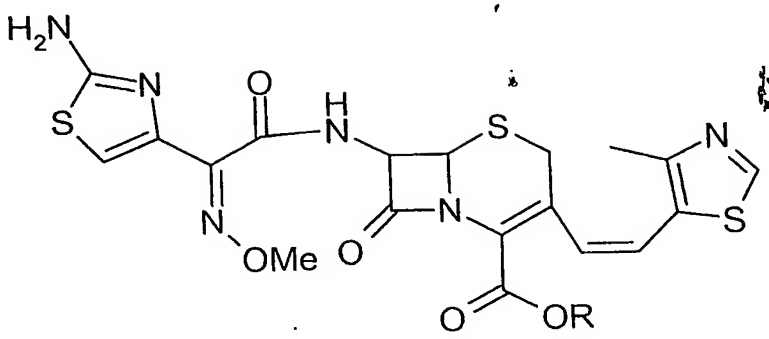
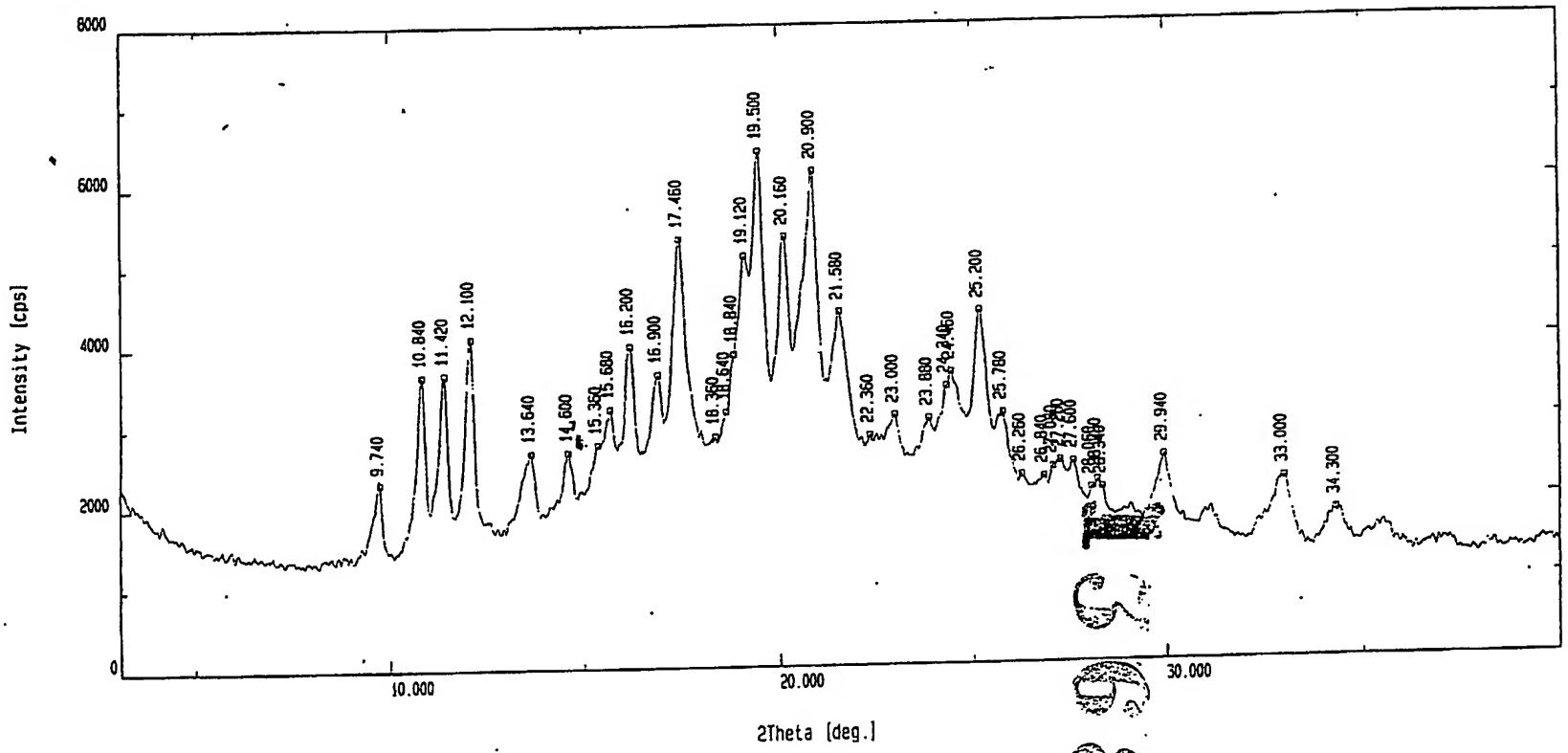


FORMULA I

For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE III

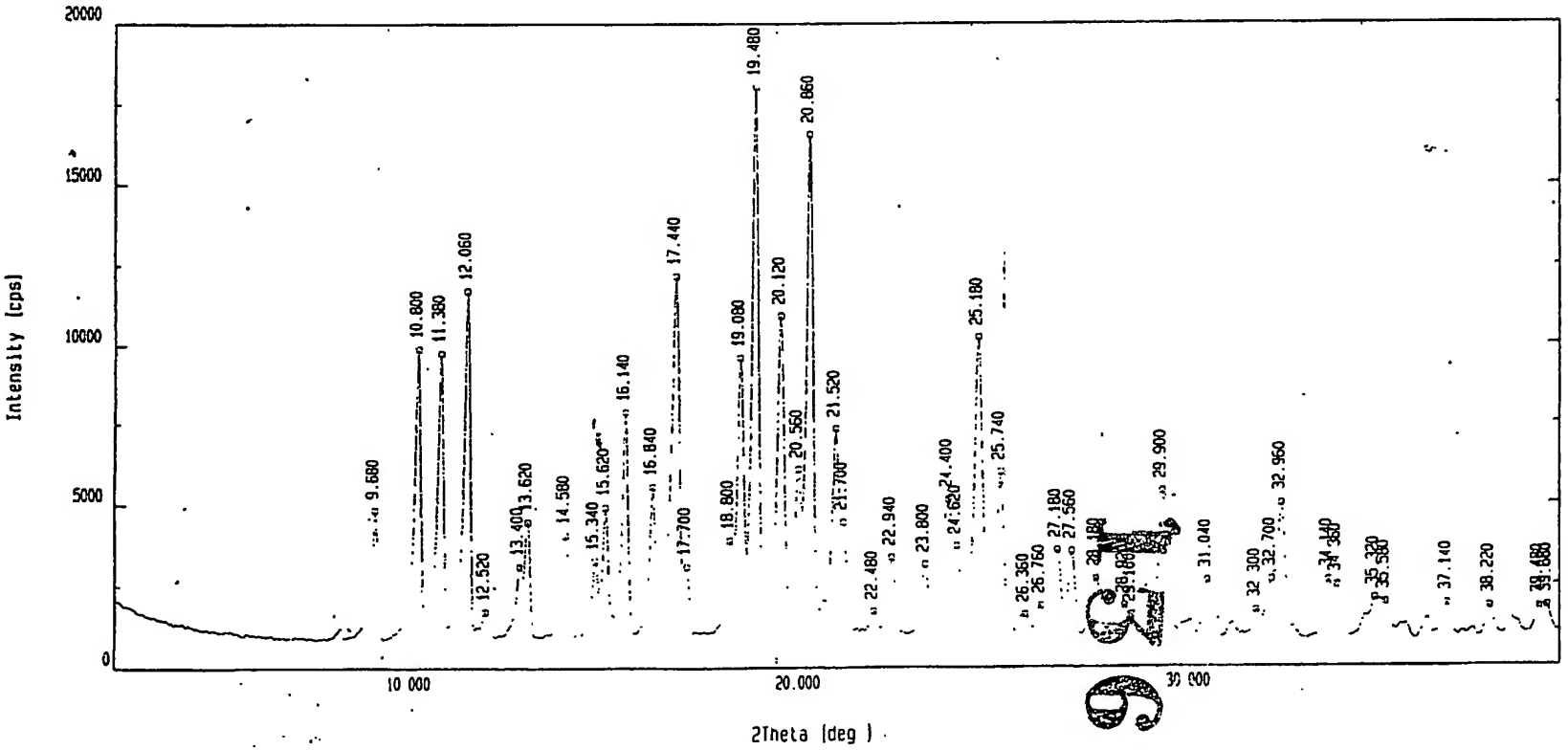


For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary

FIGURE II

ORIGINAL



For Ranbaxy Laboratories Limited

(Sushil Kumar Patawari)
Company Secretary